Renoprotective action of statin estimated from mapping renal failure in Japan

To the Editor: We have demonstrated [1, 2] the remarkable regional difference in the incidence of end-stage renal disease (ESRD) within Japan, which has an ethnically homogenous population, suggesting the presence of factors other than genetics, which may contribute to the difference. Renoprotective actions of statins, recently proposed [3], were estimated by correlating two maps of ESRD incidence and the amount of expenses prescribed on statins in Japan. Annually, the Japanese Society for Dialysis Therapy reports the numbers of patients entering maintenance dialysis in each prefecture of Japan [4]. We used the findings for 1996 to 2000 to correlate the regional ESRD distribution with regional differences in annual amounts paid for antihypertensive drugs and statins during the same 5 years (Crecon Research & Consulting, Inc., Tokyo, Japan) (Table 1). Multiple regression analysis identified converting enzyme inhibitor (F = 34.3) and statins (F = 7.1) as independently negative factors arresting the progression of nephropathies, while total antihypertensives as positive factors (F = 17.8). Renal protective actions of statins, in addition to converting enzyme inhibitors, those of which we already reported [2], were revealed by analyzing ESRD map. Our epidemiologic approaches for Japan as a whole seemed useful to estimate the renoprotective actions of certain agents that have not been clarified by large-scale clinical trials.

TAKESHI USAMI, NAOYUKI NAKAO, MICHO FUKUDA, ATSUHIRO YOSHIDA, and GENJIRO KIMURA Nagoya, Japan

Correspondence to Takashi Usami, Department of Internal Medicine and Pathophysiology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. E-mail: t-usami@med.nagoya-ct.ac.jp

REFERENCES

Inadequate group size compromises conclusions of hemodialysis graft surveillance study

To the Editor: A recent study by Ram et al [1] criticizes earlier randomized, controlled trials on their statistical validity, but itself exhibits major statistical flaws.

The authors in [1] criticize others [2] for having a “surveillance group [that] had more prior interventions than the control group.” Yet in their own study, it appears that the entry percutaneous transluminal angioplasty (PTA) rate in the control group was 2.5 times higher than the flow group (Table 1, row 2).

The authors in [1] also criticize others [3] for having a “group [that] had a high thrombosis rate because of multiple thromboses in a small number of grafts.” Yet the authors admit to this very shortcoming for their flow group, and explain that its high thrombosis rate “is misleading in that it was caused by multiple thromboses in three grafts.” The poor comparability between their groups is even more pronounced when assessing entry graft age (Ram et al [1], Table 2) where removing not three, but one graft from the control group makes it 9.6 months younger (P = 0.043) than the flow group! These disparities suggest a lack of uniformity among the three groups on the very issues being studied: PTA rate, thrombotic events (Table 1, Row 1), and graft survival (age).

The lack of group uniformity for these crucial parameters is a consequence of the small number of patients inadequate for the high values of variation coefficient ratio of standard deviation to mean value (S/M) (Table 1, rows 3 and 4). To achieve credible data, Bland [4] suggests that authors should choose the number of patients based

### Table 1. Regional differences in annual incidence of ESRD and usage of statin (1996 to 2000)

<table>
<thead>
<tr>
<th>Region</th>
<th>ESRD incidence&lt;sup&gt;a&lt;/sup&gt; million/year</th>
<th>Usage of statin&lt;sup&gt;a&lt;/sup&gt; yen/person/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hokkaido</td>
<td>257 ± 5</td>
<td>2510 ± 120</td>
</tr>
<tr>
<td>2. Tohoku</td>
<td>222 ± 5</td>
<td>2090 ± 71</td>
</tr>
<tr>
<td>3. Kanto</td>
<td>230 ± 5</td>
<td>1760 ± 80</td>
</tr>
<tr>
<td>4. Koshinetsu</td>
<td>221 ± 10</td>
<td>1780 ± 90</td>
</tr>
<tr>
<td>5. Hokuriku</td>
<td>213 ± 7</td>
<td>2430 ± 90</td>
</tr>
<tr>
<td>6. Tokai</td>
<td>235 ± 6</td>
<td>1820 ± 80</td>
</tr>
<tr>
<td>7. Kinki</td>
<td>243 ± 7</td>
<td>2040 ± 70</td>
</tr>
<tr>
<td>8. Chugoku</td>
<td>228 ± 7</td>
<td>2110 ± 100</td>
</tr>
<tr>
<td>9. Shikoku</td>
<td>267 ± 8</td>
<td>2090 ± 60</td>
</tr>
<tr>
<td>10. Kyushu</td>
<td>268 ± 5</td>
<td>1840 ± 70</td>
</tr>
<tr>
<td>11. Okinawa</td>
<td>284 ± 5</td>
<td>1090 ± 60</td>
</tr>
</tbody>
</table>

Regions are from north (1, Hokkaido) to south (11, Okinawa). Mean ± SEM. P < 0.0001 by analysis of variance (ANOVA).
Letters to the Editor

Table 1. Comparison of graft characteristics derived from Table 2 and Figure 4 of Ram et al study [1]

<table>
<thead>
<tr>
<th></th>
<th>Control group N = 34</th>
<th>Flow group N = 32</th>
<th>Stenosis group N = 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 No. of rethrombosis events(^a)</td>
<td>2</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>2 Entry PTA rate/patient year(^b) estimation from Table 2</td>
<td>1.46</td>
<td>0.58</td>
<td>0.70</td>
</tr>
<tr>
<td>3 Entry graft age days S/M</td>
<td>1.6</td>
<td>1.5</td>
<td>0.70</td>
</tr>
<tr>
<td>4 Entry no. of PTA S/M</td>
<td>1.6</td>
<td>1.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

\(^a\)Not included are rethrombosis events that occurred before Qa could be measured.
\(^b\)Entry thrombosis rates, rates of preemptive PTA (the crucial parameters of this study), and methodology of calculations were not presented by authors in Table 2 nor in Methods. The author (W.D.P.) declined to clarify. We estimated PTA rate/patient by dividing entry PTA events by entry graft age days.

We appreciate the passionate commitment of members of Transonic Corporation to their ultrasound dilution device. Nevertheless, we hope this commitment will not keep them from applying a balanced view when evaluating surveillance studies. We believe they have much to contribute to improving the management of hemodialysis accesses.

WILLIAM D. PAULSON, JACK WORK, and SUNANDA J. RAM
Shreveport, Louisiana, and Atlanta, Georgia

Correspondence to William D. Paulson, LSU Health Sciences Center, 1501 Kings Hwy, Shreveport, LA 71130.
E-mail: wpauls@lsuhsc.edu

REFERENCES
3. SANDS JJ, JABYAC PA, MIRANDA CL, KAP'SICK BJ: Intervention based on monthly monitoring decreases hemodialysis access thrombosis ASAIO J 45:147–150, 1999

Reply from the Authors

Krivitski et al [1] represent Transonic Corporation, the manufacturer of the ultrasound dilution device that is widely used to measure access blood flow (Qa). We share their disappointment that Qa surveillance did not prolong graft life in our randomized controlled trial [2]. We have the following response to their criticisms:

1. They have not accurately described the context of our comments concerning previous studies. Our intent was to show that the role of surveillance has not yet been established.
2. They claim that our study had inadequate sample size and that there was poor comparability between groups.

A. The primary end point of our study was graft survival. Our 95% CI shows that if Qa surveillance increased probability of graft survival, it was by less than 0.25 at 2 years. This result shows that if surveillance improves survival, it is modest at best, and far less than in landmark, nonrandomized studies (which have reported 4-fold improvements in survival). Krivitski et al are applying an unrealistic standard when they demand adequate sample size for all possible comparisons, whether or not they are study end points.

B. Our study used the proportional hazards model to test whether adjustment for the influence of a number of variables (graft age, etc.) affected study outcome. We reached the same conclusion: there is no evidence that surveillance prolonged graft life.

3. Their calculation of rethrombosis events is invalid since they did not include all such events. Moreover, note that the relatively high thrombosis rate in the flow group was due to failures of flow surveillance.
4. Their comparison of prestudy PTA rates is invalid since it did not take into account when PTAs occurred (PTAs just before vs. remote from study entry do not have the same significance).

We have not yet been established.

on the value of variation coefficient. This study would need at least 140 patients in each group to credibly identify differences of 30% (95th percent CI) [4]. At 32 to 35 patients per group, observed variations between groups must differ by a factor of more than 2.5 to have statistical credibility.

The fact that data of just one to three grafts reverses major statistical outcomes of a 2.3-year study gives evidence to inadequate group size in relation to the study purpose. This compromises the authors’ clinical conclusions.

NIKOLAI KRIVITSKI, SWAROOP GANTELA, and VICTOR KISLUKHIN
Ithaca, New York

Correspondence to Nikolai Krivitski, Ph.D, DSc, Senior Scientist, Transonic Systems, Inc., 34 Dutch Mill Rd., Ithaca, NY 14850.
E-mail: nikolai@transonic.com

REFERENCES